Manganese: Brain Transport and Emerging Research Needs

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Idiopathic Parkinson's disease (IPD) represents a common neurodegenerative disorder. An estimated 2% of the U.S. population, age 65 and older, develops IPD. The number of IPD patients will certainly increase over the next several decades as the baby-boomers gradually step into this high-risk age group, concomitant with the increase in the average life expectancy. While many studies have suggested that industrial chemicals and pesticides may underlie IPD, its etiology remains elusive. Among the toxic metals, the relationship between manganese intoxication and IPD has long been recognized. The neurological signs of manganism have received close attention because they resemble several clinical disorders collectively described as extrapyramidal motor system dysfunction, and in particular, IPD and dystonia. However, distinct dissimilarities between IPD and manganism are well established, and it remains to be determined whether Mn plays an etiologic role in IPD. It is particularly noteworthy that as a result of a recent court decision, methylcyclopentadienyl Mn tricarbonyl (MMT) is presently available in the United States and Canada for use in fuel, replacing lead as an antiknock additive. The impact of potential long-term exposure to low levels of MMT combustion products that may be present in emissions from automobiles has yet to be fully evaluated. Nevertheless, it should be pointed out that recent studies with various environmental modeling approaches in the Montreal metropolitan (where MMT has been used for more than 10 years) suggest that airborne Mn levels were quite similar to those in areas where MMT was not used. These studies also show that Mn is emitted from the tail pipe of motor vehicles primarily as a mixture of manganese phosphate and manganese sulfate. This brief review characterizes the Mn speciation in the blood and the transport kinetics of Mn into the central nervous system, a critical step in the accumulation of Mn within the brain, outlines the potential susceptibility of selected populations (e.g., iron-deficient) to Mn exposure, and addresses future research needs for Mn. *Key words*: iron, manganese, manganese tricarbonyl methylcyclopentadienyl (MMT), transferrin, transport. — *Environ Health Perspect* 108(suppl 3):429–432 (2000). http://ehpnet1.niehs.nih.gov/docs/2000/suppl-3/429-432aschner/abstract.html

Manganese is an abundant metal. It is ubiquitous in the environment, and it occurs in water, soil, air, and food. Its essentiality is critical throughout the life span of the mammalian organism because it serves as a necessary constituent of metalloproteins, including the mitochondrial enzymes, superoxide dismutase (SOD) and pyruvate carboxylase, and the astrocyte-specific enzyme, glutamine synthetase (GS) (1,2). In nonoccupationally exposed individuals, the major route of exposure to Mn is via food. Average intake of Mn is between 2 and 9 mg/day (for an average 70-kg person). Avocados, blueberries, nuts and seeds, seaweed, egg yolks, whole grains, legumes, dried peas, and green leafy vegetables are particularly rich in Mn as is tea. Substantial tea intake in the diet accounts for the significantly greater daily intake of Mn in Britain than in the United States (8.8 and 2.5–4 mg Mn/day, respectively). The predominant route of exposure to Mn in occupational settings is by inhalation.

Although only a small fraction of Mn accumulates in the brain, the latter is critically affected both by deficiency and excess of Mn. Mn readily crosses the blood–brain barrier (BBB) in the developing fetus, neonate, and the mature mammal (3,4). The brain normally contains only a small amount of Mn (5), and both deficiency and excess of Mn critically affect it. Seizure activity, a hallmark of Mn deficiency, is believed to result from decreased Mn–superoxide dismutase (Mn–SOD) and GS activities (6), whereas excessive exposure to Mn is associated with an irreversible central nervous system (CNS) disorder characterized by prominent psychological and neurological disturbances.

Idiopathic Parkinson's disease (IPD) represents a common neurodegenerative disorder. An estimated 2% of the U.S. population, age 65 and older, develops IPD. The number of IPD patients will increase over the next century as the baby-boomers gradually step into this high-risk age group, concomitant with the increase in the average life expectancy. While the symptoms of IPD are clearly distinct from those in manganism (see below), given the many similarities between the two disorders, the role of long-term exposure to Mn in IPD should not be immediately dismissed.

Initial symptoms associated with manganism are of psychiatric nature, and are clinically defined as *locura manganica*. These symptoms closely resemble those encountered in schizophrenics, and they include compulsive or violent behavior, emotional instability, and hallucinations. Neurological manifestations usually begin shortly (1–2 months after the first symptoms) after the appearance of those psychiatric symptoms. The neurological signs include progressive bradykinesia, dystonia, and disturbance of gait. The facial expression is somewhat fixed, and speech difficulty is frequently observed. Progressively, the patients develop slurring and stuttering speech with diminished volume and their voices become monotonous and sink to a whisper. The speech is slow and irregular, at times with a stammer. The clinical picture closely resembles several other clinical disorders collectively described as extrapyramidal motor system dysfunction and, in particular, Parkinson's disease and dystonia (7–9). At the cellular level, this condition is associated with increased Mn concentrations, primarily in those CNS areas known to contain high concentrations of non-heme iron. These areas comprise the caudate–putamen, globus pallidus, substantia nigra, and subthalamic nuclei (10,11). Nevertheless, unlike in IPD, Mn intoxication is associated with preservation of the nigrostriatal dopaminergic pathway despite clinical evidence of parkinsonian-like deficits (9). Damage to output pathways downstream to the nigrostriatal dopaminergic pathway (globus pallidus) has been implicated as a potential cause for the parkinsonism-like syndrome associated with chronic low-level Mn exposure (9). Furthermore, in manganism Lewy bodies are seldom found in the substantia nigra, but they are usually found in patients with Parkinson's disease (9).

There are a limited number of studies that address the neurological deficits of Mn exposure in children. Two studies (12,13) indicate that children who ingested Mn in the drinking water ($\geq$ 0.241 mg/L) for a minimum of 3 years performed more poorly in school as

measured by mastery in Chinese, mathematics performance, and in their overall grade average (compared with nonexposed students). The Mn-exposed children also performed more poorly on a battery of neurobehavioral tests. Mn exposure levels in these students were determined by hair analysis. It is noteworthy that no reference was made in the study (13) to levels of lead and mercury in the hair, and it is unclear if these or perhaps other xenobiotics in the drinking water (or air) may have accounted for the differences in the behavioral tests. It also appears that the researchers have not been blind to the manganese levels in the hair in two groups, hence bias in reporting and conclusions cannot be ruled out. These studies should therefore be cautiously evaluated within the context of Mn exposure and neurobehavioral effects in children.

Transport Kinetics of Mn into the CNS

Excretory pathways for Mn are well developed in the neonatal rat, and the avid retention of tracer quantities of Mn by the neonate are likely a consequence of the scarcity of this essential trace metal in its diet (11). Mn is required in a high amount during infancy and a sufficient Mn supply is critical for normal brain development (14). Approximately 80% of Mn in plasma is bound to β_1-globulin and albumin (15), and a smaller fraction of Mn is bound to transferrin (Tf). Mn binding to Tf is time dependent (3,16,17). When complexed with Tf, Mn is exclusively present in the trivalent oxidation state (18). At normal plasma Fe concentrations (0.9–2.8 µg/mL), iron binding capacity (2.5–4 µg/mL), and Tf concentration [3 mg/mL, with two metal ion-binding sites per molecule (M_r 77,000), of which only 30% are occupied by Fe^{3+}], Tf has 50 µmol/L of unoccupied Mn^{3+} binding sites. Tf receptors are present on the surface of the cerebral capillaries (19–21) and endocytosis of Tf occurs in capillaries (21). Support for receptor-mediated endocytosis of a Mn–Tf complex in cultured neuroblastoma cells was provided by Suarez and Eriksson (22).

Other ligands for Mn^{2+} must exist, however, because plasma that is saturated with Fe^{2+}, Zn^{2+}, and Cd^{2+} will bind Mn^{2+} (23). Dickinson et al. (24) have addressed the tissue distribution of injected ^{54}Mn ($MnCl_2$) in a hypotransferrinemic mouse mutant. This mouse has a mutation in the Tf gene and produces < 1% of normal (wild-type animals) Tf levels. ^{54}Mn accumulated at abnormally high levels in the Hp mouse liver, yet its distribution in the CNS was not altered. These results reveal that Tf is probably required for proper targeting of Mn from the liver to other organs, but indicate that non-Tf transport mechanisms for Mn must also exist. Unlike many other metals, Mn^{2+} does not possess high affinity for any particular endogenous ligand. There is almost no tendency for Mn^{2+} to complex to –SH groups and to amines. Not surprisingly, Mn^{2+} does not have much variation in its stability constants for endogenous complexing ligands ($\log_{10}K$ = 3, 4, 3, and 3, for glycine, cysteine, riboflavin, and guanosine, respectively, where K is the affinity constant). It is likely that minute amounts of Mn^{2+} in plasma exist, according to the mass action law, as a chloride complex. The law predicts that at a constant temperature the product of the active masses on one side of the equation when divided by the product of the active masses on the other side of the chemical equation is a constant, regardless of the amounts of each form present at the beginning of the action. While the amount of free Mn in plasma at any one time must be minute, the mass action law implies that an infinitesimal amount is always present. It also holds that if any Mn^{2+} leaves the plasma by dissolving in a lipid membrane, the protein–Mn^{2+} complex dissociates to maintain equilibrium.

The CNS distribution of Tf receptors in relationship to Mn accumulation is noteworthy. The thalamic nuclei, the pallidum, and the substantia nigra contain the highest Mn concentrations (7). Although the areas with dense Tf distribution (25) do not correspond to the distribution of Mn (or Fe), the fact that Mn-accumulating areas are efferent to areas of high Tf receptor density suggests that these sites may accumulate Mn via axonal transport (26). For example, the nucleus accumbens and the caudate–putamen—two areas that are abundantly rich in Tf receptors—provide efferent fibers to the Mn-rich areas of the ventral–pallidum, the globus pallidus, and substantia nigra (27,28).

A limited number of studies addressed the transport kinetics of Mn into the CNS. The studies are largely derived from animal models (particularly rodents). Although the rodent (specifically the rat) does not represent an optimal animal model to study the mechanisms of Mn-induced neurotoxicity, the distinction between species is not made in this review, since no evidence exists to substantiate differential transport systems for Mn in the rodent and the primate. Collectively, transport studies suggest that $MnCl_2$ enters the brain from the blood either across the cerebral capillaries and/or the cerebrospinal fluid (CSF). At normal plasma concentrations, Mn enters the CNS primarily across the capillary endothelium, whereas at high plasma concentrations, transport across the choroid plexus predominates (14,29–33).

Mn accumulates in the olfactory bulb and tubercle as well as cerebral cortex, hypothalamus, striatum, and hippocampus after intranasal injection into the nostril (34–36). Thus, when inhaled, Mn may be absorbed via the olfactory pathway. The relative amounts absorbed and the significance of this pathway for brain Mn accumulation are not accurately defined.

The impact of potential long-term exposure to low levels of MMT combustion products that may be present in emissions from automobiles has yet to be fully evaluated. Using various environmental modeling approaches, it was estimated that air levels of Mn in most urban areas in the United States would increase < 0.02 µg/m³ if MMT were used in all unleaded gasoline (37). A probability-based study involving over 900 personal exposure samples in Montreal (where MMT has been used for more than 10 years) confirmed that exposures to airborne Mn ≤ 2.5 µm in aerodynamic diameter in the general population are quite low (0.008 µg/m³–median), suggesting that airborne Mn levels in Montreal were quite similar to those in areas where MMT was not used (37). These studies also show that Mn is emitted from the tailpipe of motor vehicles primarily as a mixture of manganese phosphate and manganese sulfate and, to a lesser extent, oxides [e.g., manganese tetroxide (Mn_3O_4)] (51). Moreover, isolated particles consist of manganese, oxygen, phosphorous, and sulfur and indicate that manganese phosphate is the main constituent of the residual particles (38).

The differential distribution in rats exposed to two forms of manganese, $MnCl_2$ and MnO_2, administered by intratracheal injection, gavage, or intraperitoneal injection were studied by Roels et al. (39). When administered as MnO_2 by intratracheal injection (mimicking the inhalation route), the distribution of Mn in the CNS was similar to that of $MnCl_2$, accumulating preferentially in striatum, cortex, and cerebellum. However, Mn was found at much lower concentrations. Administration of manganese as $MnCl_2$ by gavage resulted in the same amount of blood Mn levels as intratracheal administration of Mn in the same form. However, unlike intratracheal injection, it did not lead to a significant increase of Mn levels in the cortex. These data suggest that the more soluble $MnCl_2$ salt accumulated more readily in the CNS compared with the less soluble MnO_2. Furthermore, the studies indicate that inhalation of $MnCl_2$ or MnO_2 leads to a more pronounced accumulation of Mn in the CNS compared with oral exposure. While the effect of manganese sulfate on brain levels of nicotinamide nucleotides has been addressed (40), the study lacks toxicokinetic data on the uptake of Mn into the CNS, and therefore it could not be used to contrast transport rates with other forms of Mn. Toxicology studies were also conducted by administering

manganese sulfate in feed to groups of male and female F344/N rats and B6C3F1 mice for 14 days, 13 weeks, and 2 years. However, these studies were not designed to assess any neurotoxicity that might have been expected with chronic exposure to sufficiently high doses of manganese. Nor did these studies address the accumulation of Mn in the CNS, precluding comparisons with other Mn salts (41). No other studies could be localized on the toxicokinetics of manganese phosphate and manganese sulfate (and to some extent manganese tetroxide) vis-à-vis CNS Mn accumulation. Given the impact of potential long-term exposure to low levels of MMT combustion products, it is imperative that such studies be carried out.

In summary, how and in what chemical form Mn is transported across the BBB remains to be more clearly understood. It appears that a number of transport processes are involved in the transport of Mn across the BBB:

- Facilitated diffusion (passive process where the driving force for transport is regulated by participation of transport carriers, and the gradient for transport is provided by the electrochemical potential of permeants) (32).
- Active transport (where the driving force for transport is regulated by participation of transport carriers, and exergonic chemical reactions are coupled to the permeant transport) (16,31,32).
- Tf-dependent transport (14,16). Although nonprotein-bound Mn enters the brain more rapidly than Tf-bound Mn (31,32), the question remains as to which form represents the predominant mechanism of transport in situ.

It is clear that different salts of Mn are transported at differential rates and that the route of exposure can govern the concentrations of Mn in various brain regions. With respect to Mn phosphate, Mn sulfate, and Mn tetroxide, the primary combustion products of MMT (38), no data are presently available on their transport kinetics across the BBB.

Fe Deficiency: A Potential Risk Factor for Mn Neurotoxicity

The competition between Fe and Mn for the same carrier transport system is noteworthy and bears significant implications for potential increased accumulation of CNS Mn in Fe-deficient populations. Plasma Fe overload significantly decreases the uptake of Mn across the BBB, whereas Fe deficiency is associated with increased CNS burden of Mn (3,4). In vivo, intravenous administration of ferric hydroxide–dextran complex significantly inhibits the net uptake of Mn in the CNS, and high Fe food intake reduces the concentration of Mn in the CNS (3,42).

Chemically and biochemically, Mn shares numerous similarities with Fe. For example: a) both metals are transition elements adjacent to each other in the Periodic Table; b) both carry similar valence charges (2+ and 3+) in physiological conditions; c) both have similar ionic radius; d) both strongly bind Tf (3,14,22), and e) intracellularly, both preferentially accumulate in mitochondria (43,44). Because of these similarities, it is not surprising that Mn can potentially interact directly with Fe at the cellular and subcellular levels, particularly with certain mitochondrial enzymes that require Fe as a cofactor in their active catalytic center (56). Such enzymes include aconitase, NADH–ubiquinone reductase (Complex I), and succinate dehydrogenase (45). Diets high in fat or iron have been associated with an increased risk for development of colon cancer. These two dietary factors are known to decrease Mn–SOD activity in colonic mucosa, an enzyme with antioxidative properties (46). These data are consistent with competition between these two metals and support the hypothesis that chronic Fe deficiency may lead to enhanced accumulation of Mn in the CNS, potentially leading to aberrant function. Fe deficiency, defined as an insufficient supply of Fe to the cells of the body after Fe reserves have been exhausted, is the most prevalent single nutritional deficiency, affecting over 2 billion people, mostly in the developing world. Infants and small children and adolescent, pregnant, and fertile-age women are most vulnerable (47–53). The majority of these cases result from inadequate intake of Fe. The potential for increased CNS Mn accumulation in this large population and by inference the potential health risks associated with elevated brain Mn burden, clearly represent crucial issues of exposure and susceptibility that have yet to be evaluated.

Mn: Future Research Needs

Studies on Mn transport across the BBB as well as the mechanisms of its neurotoxicity are inconclusive. The following section prioritizes research needs that are deemed necessary to define pertinent issues of Mn transport and neurotoxicity.

The intravenous injection of Mn yields slower clearance of the metal as compared to oral administration. It implies that more Mn crosses into tissues, presumably because bolus injections circumvent first-path metabolism in the liver. Although Mn transport across the BBB in its divalent form occurs in conditions where a large bolus of Mn has been injected directly into the systemic circulation, it is yet to be determined if it represents the physiologically relevant transport species. Considering that in systemic bolus studies (where Mn is injected directly into the blood),

the injected concentrations of Mn are orders of magnitude higher than those encountered physiologically, it is possible that Mn saturates binding capacities of plasma-binding proteins such as albumin and macroglobulin (3). This may lead to erroneous transport kinetics that does not represent physiological processes of Mn transport in blood upon ingestion or to occupational exposures, where in both conditions the concentrations of Mn in plasma would be expected to be significantly lower. Therefore, under experimental conditions of bolus injections into the blood stream, one cannot discount the possibility that CNS transport results from leak pathways, especially across brain capillaries in those areas that lack the zonulae occludentes of the BBB (i.e., circumventricular organs) or the choroid plexus. It should also be noted that the distribution of bolus Mn injections (where Mn is in the divalent oxidation state) is inconsistent with the results of pharmacokinetic studies of Mn distribution upon inhalation and ingestion. It is therefore crucial to address the effects on the blood of transport of Mn in its different oxidation states as well as different exposure routes at physiologically relevant concentrations of Mn. Additional knowledge gaps exist with respect to the correlation of ambient air concentrations of the combustion products of MMT and blood Mn concentrations. As pointed out earlier, ambient Mn concentrations in the Montreal area were quite similar to Mn levels in areas where MMT was not used (37,38). A critical issue to be resolved relates to the speciation of Mn in plasma, as well as to its uptake mechanism into the brain. It is of interest that Mn concentrates within the globus pallidus and striatum, areas abundantly rich in Fe, raising an intriguing question about the potential for Tf to transport Mn in its 3+ oxidation state. Studies using in vivo microdialysis can shed novel information on this issue. These studies will also facilitate regional analysis of Mn transport within the physiological range of Mn in plasma.

In vitro (cell culture) studies are needed to identify the effects of Mn on transmitter metabolism, uptake, and efflux. It is apparent that continued focus on dopaminergic innervation is necessary, given that optimal levels of striatal dopamine do not necessarily preclude the possibility of dopaminergic cell loss, representing upregulation in the function of those cells that have not succumbed to the effect of Mn. It should also be pointed out that other neurotransmitters such as γ-aminobutyric acid and glutamate are co-localized to the same brain areas and therefore may play active roles in Mn-induced neurotoxicity.

In vitro as well as in vivo studies should be conducted to address whether the toxicity of Mn is secondary to disturbances in Fe

metabolism. With a continuum of dosages, it may be possible to ascertain whether Mn is cytoprotective at low concentrations but cyto-toxic at higher concentrations. Attention should be directed both to astrocytes and oligodendrocytes because they accumulate Mn and Fe preferentially (~ 80% of total Mn is in astrocytes and the same percentage of Fe is localized within oligodendrocytes). Because both Mn and Fe share similarities in their chemistry and biochemistry, it is reasonable to postulate that the mechanisms underlying Mn distribution both in health and disease are dependent on Fe homeostasis.

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